REMARKS

Applicant has carefully reviewed and considered the Office Action mailed on October 1, 2002, and the documents cited therewith.

Claims 1-3 are amended, and claims 10-34 are withdrawn from consideration; as a result, claims 1-3, and 5-34 are now pending in this application, with claims 1-9 under examination at this time. No new subject matter has been added. The amendments are made to clarify the claims, and not for reasons relating to patentability. Therefore, the amendments are not intended to limit the scope of equivalents to which any claim element may be entitled.

Support for the amendments to claims is found throughout the specification. For example, support for the amendment to claim 1 can be found at page 7, line 4 (definition of "dho").

Support for the amendment to claim 2 is found, for example, at page 26, lines 10-12 (Dh-OLF showed an identical chromatographic retention time to the standard dihydroouabain component dho-B).

Support for the amendment to claim 3 is found, for example, at page 27, lines 10-18 (ouabain antibodies showed 2-3% cross-reactivity with dihydroouabain or Dh-OLF).

Affirmation of Election

Restriction to one of the following claims was required: Group I (claims 1-9), Group II (claims 10-20), Group III (claims 21-23), Group IV (claims 24-26), Group V (claims 27-28), Group VI (claims 30-31) and Group VII (claims 32-22).

As provisionally elected by telephone by Applicant's representative, Ann Viksnins, on September 23, 2002, Applicant elects to prosecute the invention of Group I, claims 1-9. Applicant reserves the right to later file continuations or divisions having claims directed to the non-elected inventions.

Claim Objections

The examiner objected to claims 2 and 4 because of a formality. Namely, claims 2 and 4 refer to the abbreviation "dho" without the full name of the compound being first listed. This informality has now been corrected by amendment to the claim 2.

§112 Rejection of the Claims

Claims 1-9 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the examiner indicates that the term "dihydroouabain-like factor" is indefinite, because the ordinary artisan would not know the metes and bounds of this term.

It should be noted that the terms "ouabain-like factor" (OLF) (also called "ouabain-like compound" (OLC)) are terms well-known in the art as a distinct compound. *See, e.g.*, Zhao *et al.*, *Biochemistry* 34:9893-9896 (1995). The term "dihydroouabain-like factor" (Dh-OLF) was coined to be consistent with this earlier terminology and represents a distinct compound. As used in the present application, the term "dihydroouabain-like factor" does not mean any generic compound that may be similar to dho, but a specific compound as this term is used in the published literature.

There are four related compounds of interest in this application: ouabain, dihydroouabain (dho), ouabain-like factor (OLF), and dihydroouabain-like factor (Dh-OLF). "Ouabain" is a plant-derived cardiac glycoside that inhibits the catalytic activity of Na^+, K^+-ATPase. Qazzaz et al., *Bichim et Biophys. Acta* 1472 (1999) 486-497 (*see*, Introduction). "Dihydroouabain" is synthetically made from this plant-derived ouabain, and is commonly used as a sodium pump antagonist. *Id.* Incidentally, it is now known that the compound commonly known as "dho" comprises two different biologically active isomers, dho-A and dho-B. *Id.* OLF is a mammalian cardenolide that is a counterpart to plant-derived ouabain. Qazzaz et al., *Endocrinology* 141 (2000) 3200-3209 (*see,* Introduction). "Dh-OLF" is a distinct mammalian lactone-hydrogenated ouabain-like factor found, for example, in the secretions of cultured mouse adrenal Y-J cells. *Id.* In many ways Dh-OLF structurally and functionally mimics plant-derived dho. *Id.* It is, however, structurally and functionally distinct from ouabain, OLF, and dho.

It should be noted that even though it was originally believed that ouabain and OLF were identical (*see*, Hamlyn et al., *PNAS* 88:6259-6263 (1991)), it was later discovered that these compounds were indeed different (*see*, Zhao *et al.*, *Biochemistry* 34:9893-9896 (1995)). Since rhamnoside cardiotonic steroids were not known as natural products from mammalian sources, it became important to compare these two pure isolates to determine if the same or structurally distinct compounds had been found. Zhao et al.'s results indicated that OLF and plant ouabain were different.

The present inventors have conducted comparative studies between plant-derived dho and Dh-OLF. *See*, Declaration of Dr. Roland Valdes, Jr. The data show that these compounds separate (after being mixed together or injected separately) by HPLC using reverse phase chromatography. Because they separate during these chromatography experiments, they must be structurally different. The inventors even performed the further experiment of removing the rhamnose sugar from dho and Dh-OLF, and the dihydroouabagenin-B and Dh-OLF-genin still separated differently. Thus, these experiments provide clear evidence that dihydroouabain and Dh-OLF are structurally different compounds.

The examiner also stated that the terms "similar to" and "substantial" are indefinite. These terms have been deleted from the claims, thereby rendering this rejection moot.

Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

§102 Rejection of the Claims

Claims 1-9 were rejected under 35 U.S.C. § 102(b) as being anticipated by Repenning (U.S. 3,113,128).

Repenning discloses a chemical process for generating dihydroouabain (dho) from the plant-derived starting material ouabain. As discussed above, however, there are structural and functional distinctions between dho and the Dh-OLF recited by the present claims. The process to generate dho from ouabain described by Repenning actually generates both the dho-A and dho-B isomers of dho.

The present invention is to Dh-OLF. As discussed above, Dh-OLF is a structurally distinct compound from dho, OLF or ouabain. Thus, Dh-OLF is a patentable compound.

Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 102(b) be withdrawn.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612-373-6961) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 C.F.R. § 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this 31st day of March, 2003.

Name Amy Moriarty

Signature Amy Moriarty